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09/707,087	11/06/2000	Carl H. June	RPI-034CPCN	8859

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Lahive & Cockfield
28 State Street
Boston, MA 02109

EXAMINER
LI, QIAN J

ART UNIT	PAPER NUMBER
1632	7

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Please find below and/or attached an Office communication concerning this application or proceeding.

Offic Action Summary	Application No. 09/707,087	Applicant(s) JUNE ET AL.	
	Examiner Janice Li	Art Unit 1632	

-- The MAILING DATE f this communication appears on the c ver she t with the correspondence address --

Peri d for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disp sition of Claims

4)☒ Claim(s) 1 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

The preliminary amendment filed on November 6, 2000 has been entered and assigned as Paper #6. Claims 2-31 have been canceled, claim 1 is pending and under current examination.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 1 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The methodology for determining adequacy of Written Description to convey that applicant was in possession of the claimed invention includes determining whether the application describes an actual reduction to practice, determining whether the invention is complete as evidenced by drawings or determining whether the invention has been set forth in terms of distinguishing identifying characteristics as evidenced by other descriptions of the invention that are sufficiently detailed to show that applicant was in possession of the claimed invention (*Guidelines for Examination of Patent Applications under 35 U.S.C. § 112, p 1 "Written Description" Requirement;* Federal Register/ Vol 66.

No. 4, Friday, January 5, 2001; II Methodology for Determining Adequacy of Written Description (3.)).

Claim 1 recites "a method for protecting a T cell from cell death, comprising contacting the T cell with at least one agent which augments Bcl-X_L protein level in the T cell such that the T cell is protected from cell death". The specification teaches that "the at least one agent which interacts with the T cell to increase the level of Bcl-X_L protein level includes one or more agents which interact with molecules on the surface of the T cell such as the T cell receptor and CD28", "the at least one agents which augments Bcl-X_L protein level in the T cell is an agent which acts intracellularly, for example by increasing expression of the Bcl-X_L gene" (column 14, lines 26-50). The specification provides working examples to show that anti-CD28 antibody could enhance Bcl-X_L protein expression and overexpression of Bcl-X_L could prevents Fas- and anti-CD3-induced PCD in cell culture.

Considering the breadth of the claim, it embraces a genus of agents that could interact with T cells in many different ways, such as via a cell surface receptor, or via a co-stimulatory signal. However, such agents essential for practice the invention are only defined by the effects rather than the chemical or physical structures. T cell receptors encompass many types of CD receptors, MHC receptors, cytokine and chemokine receptors, for example; and each subtype of T cells have their own distinct receptor. The specification fails to teach, apart from CD28, which T cell receptor and co-stimulator would increase or augment the Bcl-X_L expression intracellularly upon activation, and it fails to teach the structure-function relationship of CD28 and the genus

of the receptors and co-stimulators that enhance Bcl-X_L expression; it fails to teach what other agent the claim may embrace which would enhance intracellular Bcl-X_L expression.

The Revised Interim Guidelines state "THE CLAIMED INVENTION AS A WHOLE MAY NOT BE ADEQUATELY DESCRIBED IF THE CLAIMS REQUIRE AN ESSENTIAL OR CRITICAL ELEMENT WHICH IS NOT ADEQUATELY DESCRIBED IN THE SPECIFICATION AND WHICH IS NOT CONVENTIONAL IN THE ART" (Column 3, page 71434), "WHEN THERE IS SUBSTANTIAL VARIATION WITHIN THE GENUS, ONE MUST DESCRIBE A SUFFICIENT VARIETY OF SPECIES TO REFLECT THE VARIATION WITHIN THE GENUS", "IN AN UNPREDICTABLE ART, ADEQUATE WRITTEN DESCRIPTION OF A GENUS WHICH EMBRACES WIDELY VARIANT SPECIES CANNOT BE ACHIEVED BY DISCLOSING ONLY ONE SPECIES WITHIN THE GENUS" (Column 2, page 71436).

The term "at least one agent" is obvious generic to a considerable number of agents that could interact with a T cell and enhance Bcl-X_L expression. However, the specification fails to provide an adequate description to teach the chemical structures or the structure-function relationship of these agent with regard to their function as enhancing Bcl-X_L expression, and accordingly does not provide a reasonable guide for those seeking to practice the invention.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116).

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481, 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

In analyzing whether the written description requirement is met for the claimed subject matter as a genus of agents that enhance Bcl-X_L expression, a representative number of species has to be disclosed by their complete sequences, structure, and other relevant identifying characteristics. The claimed genus encompasses any agent, which interacts with T cells and enhances Bcl-X_L expression, thus encompassing an uncountable number of possible agents, known or unknown. Considering the potential agents that would be encompassed by the claims, the exemplary embodiments are not the representative species of the genus.

In view of these considerations, a skilled artisan would not have viewed the teachings of the specification as sufficient to show that the applicant was in possession of the claimed invention commensurate to its scope because it does not provide adequate written description for the broad class of *all* molecules that interact with T cells and enhance Bcl-X_L expression. Therefore, only the described anti-CD28 antibody and the Bcl-X_L expression vector meet the written description provision of 35 U.S.C. §112, first paragraph.

Claims 1 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for augmenting Bcl-X_L protein level in a T cell

comprising contacting the T cell with a nucleic acid encoding Bcl-X_L or an anti-CD28 antibody in culture, does not reasonably provide enablement for eliciting such response in any T cell and by any agent *ex vivo* or *in vivo*. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

There are many factors to be considered when determining whether the disclosure satisfy the enablement requirements and whether undue experimentation would be required to make and use the claimed invention (see *In re Wands*, 858 F. 2d 731, 737, 8 USPQ 2d 1400, 1404, 1988). These factors include but are not limited to the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability of the art, the breadth of the claims, and amount of direction provided.

Considering the breadth of the claim, it embraces protecting T cell death using a genus of agents that could interact with T cells in many different ways *in vitro and in vivo*. However, the specification fails to teach the common attribution of such agent, or how to identify these agents. The circular teaching of the "at least one agent" (column 14, lines 26-50) is an invitation to further experimentation rather than an adequate description of the recited agent, accordingly does not provide a reasonable guide for those seeking to practice the invention. Further, the specification fails to provide an enabling disclosure as to the issues associated with in vivo delivery of the broad class of agents. For example, how to deliver the broad range of agents specifically to T cells without affecting other cells in an in vivo setting.

In view of the state of the art and the levels of those skilled in the art, it is known in general according to various *in vitro* experimentation that Bcl-X_L is associated with the resistance to growth factor-dependent cell death (*Boise et al,* Cell 1993;75:597-608), to immune suppressant-induced and protein synthesis inhibitor-induced cell death (*Gottschalk et al*, Proc. Natl. Acad. Sci. USA). However, the art is still unpredictable with regard to particular cell types and agents that enhance Bcl-X_L levels. For example, *Boise et al* teach that six hours of stimulation with PMA and ionomycin had no effect on bcl-x mRNA expression in double-positive thymocyte populations but induced a dramatic increase in bcl-x mRNA expression in both single-positive thymocytes and peripheral blood T cells (page 603, 1st paragraph). *Gottschalk et al* teach that Cyclosporin A, FK-506, and rapamycin could prevent PCD in T-cell hybridomas and thymocytes, but induce PCD in B cells (abstract). As taught in the instant specification, anti-CD3 antibody would induce T cell apoptosis while anti-CD28 would protect T cell from death. Furthermore, preventing PCD by Bcl-X_L expression vector and anti-CD28 antibody have not been a routine practice in an *in vivo* setting in the relevant art.

Thus, it is evident that the skilled practitioner in the art while acknowledge the potential target of Bcl-X_L, it is not routine nor acceptable for the genus of agents enhanicing Bcl-X_L expression, or for *in vivo* use of such agents in preventing T cell from PCD. Therefore, it is incumbent upon applicants to provide an enabling disclosure for the recited use within the specification. However, the specification fails to provide an enabling disclosure commensurate to the scope of the claim.

Thus, it is evident that at the time of the invention, the skilled practitioner in the art, while acknowledging the significant potential of enhancing Bcl-X_L for preventing PCD, still recognized that such practice was neither routine nor accepted, and awaited significant development and guidance for its practice. Therefore, it is incumbent upon applicants to provide sufficient and enabling teachings within the specification for such therapeutic regimen. Based upon the limited disclosure, the unpredictability of the art, the level of the skill, and the breadth of the claims, one skill in the art would have been required to perform undue experimentation to practice the invention.

Therefore, in view of the limited guidance, the lack of predictability of the art, and the breadth of the claims, one skill in the art could not practice the invention without undue experimentation as they are broadly claimed.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.
>
> (f) he did not himself invent the subject matter sought to be patented.

Claim 1 is rejected under 35 U.S.C. 102(e) as being anticipated by *Thompson et al* (US 6,303,331).

Claim 1 recites "a method for protecting a T cell from cell death, comprising contacting the T cell with at least one agent which augments Bcl-X_L protein level in the T cell such that the T cell is protected from cell death".

Thompson et al teach a method for inhibiting cell death in a cell in vitro comprising contacting the intended cells for protection with an effective amount of a polynucleotide encoding a Bcl-X_L polypeptide operably linked to a promoter, whereby expression of said bcl-XL polypeptide inhibits programmed cell death of said cell, wherein the cell is a lymphocyte, a CD4 cell (claims 1, 7, 8). Because a CD4 cell is a T cell, and contacting the T cell with said polynucleotide augments Bcl-X_L protein level in the T cell, thus, *Thompson et al* clearly anticipate the instant claims.

Claim 1 is rejected under 35 U.S.C. 102(f) because the applicant did not invent the claimed subject matter.

This application has a different inventive entity with a single common inventor as that of US Patent 6,303,331. Because claim 1 of the instant application is anticipated by the claims 1, 7, 8 of the cited patent, the inventive entity on the instant application appears to be unclear with regard to who is the real inventor.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the

invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claim 1 is rejected under 35 U.S.C. 103(a) as being unpatentable over *Boise et al* (Cell 1993;75:597-608), and in view of *Choi et al* (Eur J Immunol 1995:25:1352-57).

Claim 1 recites "a method for protecting a T cell from cell death, comprising contacting the T cell with at least one agent which augments Bcl-X_L protein level in the T cell such that the T cell is protected from cell death".

Boise et al teach that "both activated T cells and double-positive thymocytes selectively express the form of bcl-x that enhances the dependence of the cell on exogenous signals to prevent apoptosis", they later teach that "Bcl-X_L is the form that mediate significant resistance to growth factor-dependent cell death". They contact a plasmid encoding human Bcl-X_L or bcl-2 or both with a IL-3 dependent cell line, and observe cell survival after IL-3 deprivation (figure 5), they conclude that "The combination of the two vectors was no better at preventing apoptotic cell death than bcl-xl alone. This suggests that bcl-xl plays a major role in regulating the dependence of cells on continuous exogenous signals to prevent cell death" (page 604, left column). Although *Boise et al* do not teach contacting T cells with bcl-xl vector in the reported experiments, it would have been obvious to one of ordinary skill in the art seeking to improve T cell survival, at the time the invention was made, to modify the methods taught by *Boise et al,* by simply substituting the IL-3 dependent cells with T cells with a reasonable expectation of success. Thus, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claim 1 is rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 7, and 8 of U.S. Patent No. 6,303,331.

Although the conflicting claims are not identical, they are not patentably distinct from each other because claim 1 of the present application and claims 1, 7 and 8 of the cited patent are each drawn to a method for protecting a T cell from cell death, they both comprising the steps of contacting the T cell with at least one agent which augments Bcl-X_L protein level in the cell.

The processes of the present application and the cited patent differ one from the other in that "T cell" is recited in two dependent claims in the cited patent. Further, the claim of the present application embraces the claims of the cited patent because the instant "one agent" embraces the nucleic acid encoding Bcl-X_L in the cited patent.

Accordingly, the claimed processes in the cited patent and the present application are obvious variants.

Therefore, the inventions as claimed are co-extensive.

Claim 1 is rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, and 3 of U.S. Patent No. 6,143,291. Although the conflicting claims are not identical, they are not patentably distinct from each other because claim 1 embraces claims 1 & 3 of the cited patent.

Claim 1 of the present application and claims 1 and 3 of the cited patent are each drawn to a method for protecting/inhibiting a T cell from cell death, they both comprising the steps of contacting the T cell with at least one agent which augments bcl-XL protein level in the cell.

The processes of the present application and the cited patent differ one from the other in that "T cell" is virally infected in the cited patent. However, the claim of the present application embraces the claims of the cited patent because "T cell" embraces virally infected T cell, and the instant "one agent" embraces "a nucleic acid molecule comprising a gene encoding a human Bcl-X_L" in the cited patent.

Therefore, the inventions as claimed are co-extensive.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Q. Janice Li whose telephone number is 703-308-7942. The examiner can normally be reached on 8:30 am - 5 p.m., Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Karen M Hauda can be reached on 703-305-6608. The fax numbers for the organization where this application or proceeding is assigned are 703-308-8724 for regular communications and 703-308-4242 for After Final communications.

Any inquiry of formal matters can be directed to the patent analyst, Kay Pinkney, whose telephone number is (703) 305-3553.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1235. The faxing of such papers must conform to the notice published in the Official Gazette 1096 OG 30 (November 15, 1989).

Q. Janice Li
Examiner
Art Unit 1632

QJL
November 26, 2001

JAMES KETTER
PRIMARY EXAMINER